Anemia in Chronic Kidney Disease

by

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Abstract

Background: Anemia is a common complication in patients with chronic kidney disease (CKD), significantly impacting their quality of life and prognosis. This study aims to evaluate the prevalence and hematological characteristics of anemia among CKD patients.

Methods: In this retrospective study, medical records of 65 patients diagnosed with CKD at the Iraq Specialist Laboratory, Baquba, Iraq, from December 1st, 2023, to January 14th, 2024, were analyzed. Data on hematological parameters, including Red Blood Cell (RBC) count, Hemoglobin (HB), Mean Corpuscular Volume (MCV), Hematocrit (HCT), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC), were collected. Comparative analysis based on sex was performed using t-tests.

Results: All 65 patients with CKD had anemia. The overall mean values were: RBC 3.05 (SD: 0.58), HB 8.1 g/dL (SD: 1.3), MCV 87.5 fL (SD: 8.2), HCT 26.5% (SD: 4.4), MCH 26.8 pg (SD: 2.9), and MCHC 30.7 g/dL (SD: 0.9). Comparative analysis revealed no statistically significant differences in hematological parameters between male and female patients ($p > 0.05$).

Conclusion: This study highlights the universal prevalence of anemia among CKD patients in Baquba, Iraq. Despite minor variations, hematological parameters did not differ significantly between sexes. These findings underscore the need for comprehensive management of anemia in all CKD patients, regardless of gender. This study contributes to the understanding of anemia's hematological profile in CKD patients in this region, aiding in better clinical management and treatment strategies.

CHAPTER ONE

INTRODUCTION

Introduction

Anemia of Chronic Renal Disease, or Anemia of Chronic Kidney Disease (CKD), is a type of normocytic, normochromic, hypoproliferative anemia. It is often linked to unfavorable outcomes in individuals with chronic kidney disease and raises the risk of mortality (1). Anemia is prevalent in Chronic Kidney Disease (CKD). According to Hazmi et al., nearly 50% of CKD patients with a creatinine level of 2 mg/dL have a hematocrit value below 36% (2). In patients with an estimated glomerular filtration rate (eGFR) less than 30 mL/min per 1.73 m^2, up to 90% of them experience anemia, with the majority having hemoglobin levels below 10 g/dL. Both eGFR and serum creatinine levels have been used as indicators of kidney function in clinical practice, and their correlation with hematocrit levels is well-established (3).

In progressing Chronic Kidney Disease (CKD), the main reason for reduced red blood cell (RBC) production is the loss of renal parenchyma. The shrinking and scarring of the kidney lead to a decrease in the number of type I dendritic cells, which play a key role in producing erythropoietin, the hormone responsible for RBC production (4). Erythropoietin is the primary factor that stimulates the production of red blood cells (RBCs) in the bone marrow, a process known as erythropoiesis. In individuals with Chronic Kidney Disease (CKD), persistent inflammation causes the retention of iron in storage cells. These cells encompass duodenal enterocytes, hepatocytes, adipocytes, and macrophages within the reticuloendothelial system (5,6). The reduced lifespan of red blood cells (RBCs) is due to the buildup of uremic toxins and heightened production of free radicals (7,8).

Aim and Objectives

Aim

The aim of this study is to investigate the prevalence and hematological parameters associated with anemia in individuals with chronic kidney disease (CKD) and to explore potential gender-based differences in these parameters among CKD patients.

Objectives:

1. To determine the overall prevalence of anemia in the study population of CKD patients.
2. To assess the mean values and standard deviations of key hematological parameters (RBC, HB, MCV, HCT, MCH, and MCHC) in the study population of CKD patients.
3. To investigate if there are statistically significant differences in hematological parameters between male and female CKD patients.

CHAPTER TWO

LITERATURE REVIEW

Literature review

Definition of anemia

Anemia is characterized by a decrease in red blood cells (RBCs), and it's a symptom rather than a standalone diagnosis, indicating an underlying condition. The onset of symptoms in anemia depends on its cause, how quickly it develops, and other health issues the patient may have, particularly cardiovascular diseases. Symptoms typically become noticeable when hemoglobin levels fall below 7.0 g/dL (9).

Normal hemoglobin (Hgb) levels vary slightly among different groups but generally fall within these ranges (9):

- Men: 13.5 to 18.0 g/dL
- Women: 12.0 to 15.0 g/dL
- Children: 11.0 to 16.0 g/dL
- Pregnant women: Over 10.0 g/dL, varying by trimester.

Anemia of Chronic Kidney Disease (ACKD) is characterized by normocytic and normochromic red blood cells (RBCs), meaning that the average RBC volume falls within the range of 80-100 femtoliters (fL) and the central pallor of the RBC, as seen on a peripheral smear, occupies less than one-third of the RBC's diameter. To diagnose this type of anemia, both a complete blood count (CBC) and a peripheral smear are required to confirm its presence and observe its specific characteristics (3).

Etiology

Anemia in chronic renal disease has multiple causes, with the primary factor being reduced production of erythropoietin (EPO), the hormone responsible for stimulating the production of red blood cells. Recent research has connected the

decline in erythropoietin levels to the downregulation of hypoxia-inducible factor (HIF), a transcription factor that controls the expression of erythropoietin genes (10). Additional mechanisms contributing to anemia in chronic renal disease include (11):

1. Uremia, which can lead to abnormal red blood cell (RBC) shape and subsequent hemolysis.

2. Deficiency in folate and vitamin B12.

3. Iron deficiency.

4. Bleeding tendencies due to dysfunctional platelets.

5. Occasionally, blood loss can occur during hemodialysis.

In certain conditions, such as glomerulopathy and malignant hypertension, damaged blood vessels within the kidney can cause red blood cell (RBC) fragmentation. This process worsens anemia, which is why anemia can be especially severe in renal glomerulopathies, including glomerulonephritis and diabetic nephropathy, regardless of the level of kidney dysfunction (1).

Epidemiology

This condition typically arises after a significant decline in kidney function, usually when the glomerular filtration rate (GFR) drops to less than 60 mL/min/1.73 m^2, representing a loss of more than 50 percent of kidney function (12). Anemia in chronic kidney disease (CKD) tends to become more severe as the disease advances. At least 90% of individuals who require dialysis treatment for CKD will eventually develop anemia of chronic disease (1).

Anemia in chronic renal disease is linked to a lower quality of life, reduced kidney function over time, higher rates of illness and death, and elevated healthcare expenses (13). Numerous studies indicate that the occurrence of anemia in non-dialysis dependent (NDD) chronic kidney disease (CKD) can reach up to 60%

(1). Anemia becomes more common and more severe as the estimated glomerular filtration rate (eGFR) decreases. Data from the National Health and Nutrition Examination Survey (NHANES) in 2007-2008 and 2009-2010 support this trend (14) which found that anemia was twice as prevalent in Chronic Kidney Disease (CKD) patients compared to the general population (15). Recent data from the CKD Prognosis Consortium also confirmed similar findings regarding the prevalence of anemia in Chronic Kidney Disease (CKD) patients (16).

Pathophysiology

Anemia in Chronic Kidney Disease (CKD) can result from circulating inhibitors that impede erythropoiesis due to uremia. However, it's important to note that some studies have challenged this idea since no specific inhibitors have been conclusively identified (17). The reduced lifespan of red blood cells, as seen in radioisotope labeling studies, is another contributing factor to anemia in Chronic Kidney Disease (CKD) (18). Nutritional deficiencies, such as those related to vitamin B12 and folate, stemming from dialysate losses or reduced appetite, are not very common nowadays among hemodialysis patients. This is largely because nutrients are routinely supplemented in these patients' treatment regimens (1).

Recent research has highlighted the significant role of disrupted iron regulation in the development of anemia in chronic renal disease. The body maintains systemic iron levels by controlling the absorption of iron from the gastrointestinal tract and releasing it from storage locations like reticuloendothelial macrophages and the liver (19). Chronic Kidney Disease (CKD) patients experience heightened iron losses, averaging between 1 to 3 grams annually in those on hemodialysis. This is primarily due to chronic bleeding caused by uremia-associated platelet dysfunction, blood retention in the dialysis equipment, and frequent blood draws. CKD patients are at substantial risk of actual iron deficiency, and as a result, iron supplementation is a crucial component of their treatment. Hemodialysis patients

often struggle with absorbing dietary iron, which is why intravenous iron is the preferred treatment approach (20).

Diagnosis

The clinical presentation of anemia in chronic renal disease resembles anemia from other causes. Patients typically experience symptoms like shortness of breath, fatigue, weakness, headaches, reduced concentration, dizziness, and decreased exercise capacity. Observable signs may include pale skin and conjunctiva, respiratory distress, increased heart rate, chest pain (particularly in severe cases), and occasionally, heart failure, which is more common with chronic and severe anemia (21).

Common diagnostic tests for anemia in chronic renal disease include a complete blood count (CBC) with differential, peripheral smear, iron indices (iron, ferritin, total iron-binding capacity, transferrin saturation), and assessments of iron, vitamin B, and folate levels, which are initially conducted to rule out other reversible causes of anemia (22). Thyroid function tests may also be performed to rule out alternative causes of hypoproliferative normocytic anemia. CBC and peripheral smear typically reveal normocytic normochromic anemia and peripheral reticulocytopenia. It's important to note that in CKD patients, high serum ferritin levels due to chronic inflammation can inaccurately reflect the degree of iron deficiency, necessitating adjusted cutoffs for assessing iron responsiveness, especially in dialysis patients (22).

The DRIVE study revealed that intravenous iron therapy is advantageous for dialysis patients, even when their ferritin levels are as high as 1200 ng/mL, provided that their transferrin saturation is below 30% (23). Measuring serum erythropoietin levels is not recommended in Chronic Kidney Disease (CKD) because they do not serve as an indicator of anemia originating from the kidneys. In CKD, there is a phenomenon known as "relative erythropoietin deficiency,"

where erythropoietin levels inappropriately rise considering the severity of anemia, making them an unreliable marker of renal-related anemia (24).

Treatment / Management

The advancement of recombinant erythropoietin (EPO), followed by erythropoiesis-stimulating agents (ESAs), brought about a revolutionary shift in the management of anemia in Chronic Kidney Disease (CKD) (1). Initially introduced to reduce the need for blood transfusions, erythropoietin and erythropoiesis-stimulating agents (ESAs) were quickly recognized for their additional benefits. These include enhanced survival and quality of life, improved cardiac function and reduced mortality, fewer hospitalizations, and lower healthcare costs in patients with Chronic Kidney Disease (CKD) and anemia (25,26).

In the management of anemia in Chronic Kidney Disease (CKD), two commonly used erythropoiesis-stimulating agents (ESAs) are recombinant human erythropoietin and darbepoetin alfa. They exhibit similar effectiveness and side effect profiles, with the key distinction being darbepoetin alfa's longer half-life, allowing for less frequent dosing (27,28).

KIDGO guidelines advise ESAs based on hemoglobin levels. Non-dialysis CKD patients receive them for hemoglobin below 10 g/dL, with adjusted dosing. Dialysis patients use ESAs when hemoglobin is 9-10 g/dL, with specific schedules. Common side effects include seizures, hypertension, clotting, cancer progression, and increased cancer-related mortality (1). Trials show higher mortality, thrombosis, and adverse cardiovascular events in CKD patients using ESAs for target hemoglobin greater than 11 g/dl, regardless of dialysis need (29).

CKD patients face iron deficiency due to impaired absorption, chronic bleeding, and frequent phlebotomy. Iron supplementation is crucial for treatment, with intravenous iron preferred in hemodialysis patients (1). KIDGO recommends

target transferrin saturation of 20-30% and ferritin level of 100-500 ng/mL for CKD patients, and 30-50% and ferritin level of 200-500 ng/mL for ESRD patients (30).

CHAPTER THREE

PATIENTS AND METHODS

Patients and methods

Study Design and Setting

This study was conducted to evaluate anemia in patients with chronic kidney disease. The data were meticulously collected from medical records at the Iraq Specialist Laboratory in Baquba, Iraq. This retrospective study spanned a period from December 1st, 2023, to January 14th, 2023.

Data Collection

The primary source of data was the medical records archived at the Iraq Specialist Laboratory. These records provided comprehensive details on the patients' hematological parameters, crucial for assessing anemia in the context of chronic kidney disease.

Study Population

The study involved a total of 65 patients who had been diagnosed with chronic kidney disease. These patients were identified based on their medical history and laboratory test results. The inclusion criterion was a confirmed diagnosis of chronic kidney disease, while the exclusion criteria included any other major hematological disorders or conditions that could independently affect the hematological parameters.

Variables and Measurement

The key variables measured from the medical records were:

1. **Demographic Information**: Age and sex of the patients.
2. **Hematological Parameters**: Red Blood Cell (RBC) count, Hemoglobin (HB) concentration, Mean Corpuscular Volume (MCV), Hematocrit (HCT), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC).

These parameters were obtained using standard laboratory techniques and equipment, ensuring accuracy and reliability.

Statistical Analysis

Data analysis was performed using appropriate statistical software. Descriptive statistics were used to summarize the demographic data and hematological parameters. This included calculating means, standard deviations, and percentages for various variables.

For comparing hematological parameters between male and female patients, a t-test was used. The significance level was set at a p-value of >0.05. The results were presented in tabular form to provide a clear and concise comparison.

Ethical Considerations

The study adhered to ethical standards, ensuring confidentiality and privacy of patient information. Since the study involved the use of existing medical records and did not entail any direct interaction with patients or alterations in their management, informed consent was not deemed necessary. The study protocol was reviewed and approved by the relevant institutional review board.

CHAPTER FOUR

RESULTS

Results

Our study included a total of 65 participants. The distribution by sex was nearly balanced, with 31 females (47.7%) and 34 males (52.3%). Every participant in this study was diagnosed with anemia, representing 100% of the population (Table 1).

Table 1: Descriptive statistic of study population (N=65)

Variable		Count	%
Sex	**Female**	31	47.7%
	Male	34	52.3%
Anemia		65	100%

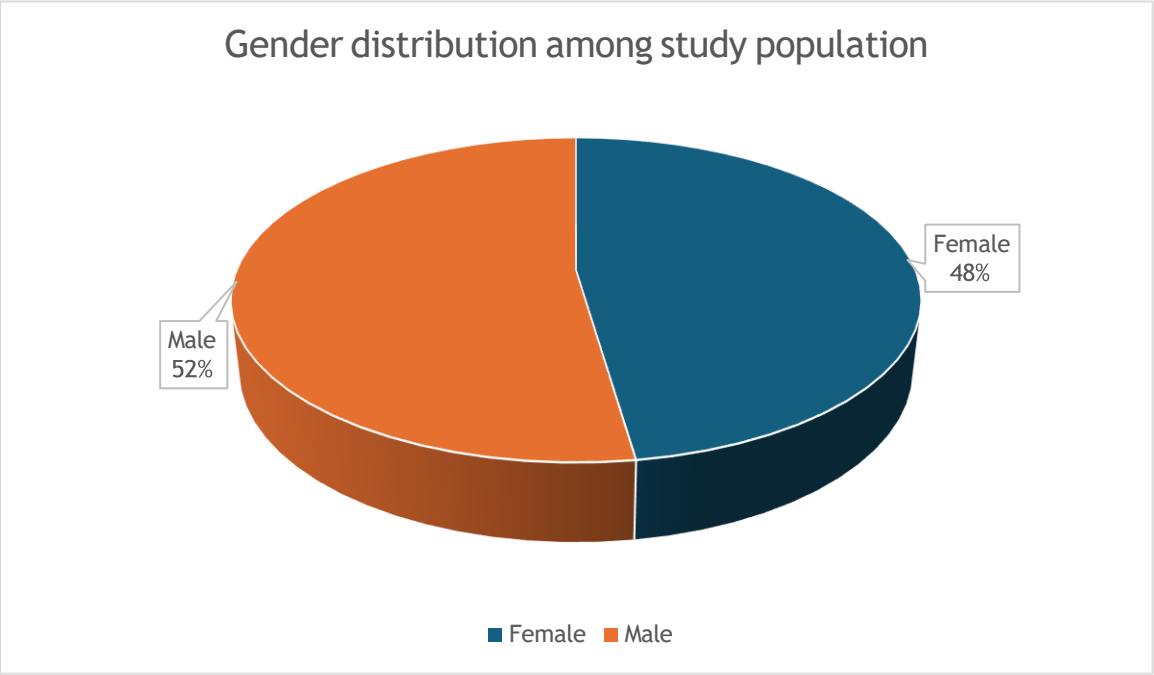

Figure 4.1: Gender distribution among study population

The average values for various hematological parameters were analyzed for the entire study population. The mean red blood cell (RBC) count was 3.05 (SD: 0.58), while the mean hemoglobin (HB) concentration was 8.1 g/dL (SD: 1.3). The mean corpuscular volume (MCV) was 87.5 fL (SD: 8.2), the hematocrit (HCT) was 26.5% (SD: 4.4), mean corpuscular hemoglobin (MCH) was 26.8 pg

(SD: 2.9), and the mean corpuscular hemoglobin concentration (MCHC) was 30.7 g/dL (SD: 0.9) (Table 2).

Table 2: Hematological parameters of study population

Variable	Mean	SD
RBC	3.05	0.58
HB	8.1	1.3
MCV	87.5	8.2
HCT	26.5	4.4
MCH	26.8	2.9
MCHC	30.7	0.9

RBC count was identical for both sexes, with a mean of 3.05. The standard deviation was slightly higher in females (SD: 0.61) compared to males (SD: 0.55).The mean HB level in females was 8.4 g/dL (SD: 1.5) compared to 8.0 g/dL (SD: 1.1) in males.MCV was higher in females (88.7 fL, SD: 6.2) than in males (86.4 fL, SD: 9.6).Females had a slightly higher mean HCT (27.1%, SD: 5.2) than males (26.0%, SD: 3.5). MCH was also higher in females (27.3 pg, SD: 2.2) compared to males (26.4 pg, SD: 3.5). MCHC was marginally higher in females (30.8 g/dL, SD: 0.7) than in males (30.6 g/dL, SD: 1.0). In all cases, the differences in hematological parameters between males and females were not statistically significant, as indicated by the p-values being greater than 0.05.

Table 3: Hematological parameters of between male and female

Variable	Sex				P-value
	Female		Male		
	Mean	SD	Mean	SD	
RBC	3.05	0.61	3.05	0.55	>0.05
HB	8.4	1.5	8.0	1.1	>0.05
MCV	88.7	6.2	86.4	9.6	>0.05
HCT	27.1	5.2	26.0	3.5	>0.05
MCH	27.3	2.2	26.4	3.5	>0.05
MCHC	30.8	0.7	30.6	1.0	>0.05

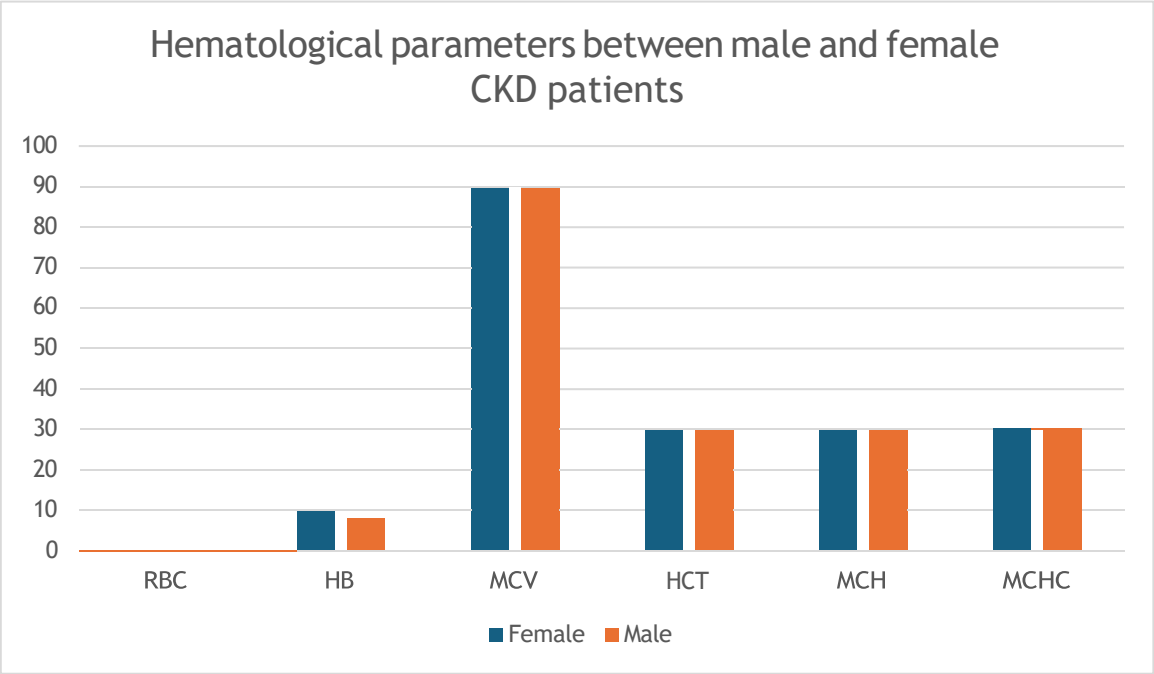

Figure 4.2: Hematological parameters between male and female CKD patients

CHAPTER FIVE

DISCUSSION

Discussion

The findings highlight the prevalence and characteristics of anemia in this patient group, with 100% of the study population being anemic. This is consistent with the literature indicating that anemia is a frequent complication in CKD, occurring in over 90% of patients undergoing renal replacement therapy (31). These levels of HB are indicative of mild to moderate anemia, which is known to impact organ function and increase risks like cardiovascular disease, faster renal failure deterioration, and mortality (32). Humudat (2023) reported anemia in 100% of hemodialysis patients with CKD (33), which is consistent with the universal anemia prevalence in our study population.

Our study's mean RBC count (3.05) is in line with findings from various studies. For instance, Behera (2020) observed significantly lower RBC counts in CKD patients compared to controls, indicating a trend of reduced RBC in CKD (34). Our mean HB value (8.1 g/dL) is indicative of moderate anemia, similar to findings by Pandian et al. (2016), who reported moderate anemia in both pre- and post-dialysis patients (35). Our mean MCV, MCH, and MCHC values are within normal ranges but at the lower end, consistent with the normocytic normochromic anemia typically seen in CKD as reported in multiple studies (36).

Interestingly, our study found no significant difference in hematological parameters between male and female patients. which is in agreement with the broader literature. Studies such as the one conducted by Lau et al. (2015) did not find gender to be a significant predictor of anemia in CKD (37). This finding is vital because it suggests that gender may not be a significant determinant of anemia severity in CKD, contrary to the general population where women tend to have lower hemoglobin levels due to factors like menstruation and pregnancy (38). Other studies demonstrated that women do indeed get affected more severely by chronic kidney disease in terms of anemia development (39).

The study's limitations include a small sample size and a single-center design, which may limit the generalizability of the findings. Future research should aim to include a larger, more diverse population and explore the impact of interventions like iron supplementation and erythropoiesis-stimulating agents on anemia in CKD patients.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

Conclusion and Recommendations

Conclusion

This study thoroughly examined anemia in individuals with chronic kidney disease (CKD), encompassing a balanced cohort of 65 participants, divided almost equally between males and females. The primary finding is that anemia is a universal complication in our study group of CKD patients. Hematological parameters, including RBC, HB, MCV, HCT, MCH, and MCHC, were carefully analyzed. While there were slight variations in these parameters between males and females, none of these differences reached statistical significance, suggesting a consistent impact of CKD on anemia regardless of sex.

Recommendations

1. Given the high prevalence of anemia among CKD patients, regular monitoring of hematological parameters is crucial. This should include not only HB levels but also RBC, MCV, HCT, MCH, and MCHC, to ensure comprehensive management of anemia.
2. Although the study didn't find significant sex-based differences in hematological parameters, individual variances suggest the need for personalized treatment plans. Tailoring anemia treatment to individual patient needs could optimize outcomes.
3. Despite the lack of significant differences in this study, further research may explore whether there are subtler sex-based variations in anemia among CKD patients that could influence treatment approaches.
4. Alongside medical treatment, nutritional and lifestyle interventions should be emphasized. A focus on diets rich in iron, folic acid, and vitamin B12, and addressing factors like smoking and alcohol consumption, could be beneficial.
5. Educating patients about the importance of managing anemia and adherence to treatment protocols is vital. Support groups or counseling may be beneficial in improving patient outcomes and quality of life.
6. Healthcare policies should support regular screening and comprehensive management of anemia in CKD patients. Enhancing access to care and affordability of treatments is also essential.